RHÔNE-POULENC

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September 10, 1999

Federal Express #8019 7908 4558

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: **Docket No. 99N-0193**
Comments on FDA's Proposed Rule
"Supplements and Other Changes to an Approved Application"

Dear Sir or Madam:

Reference is made to the Federal Register Notice [64 FR 34608] dated June 28, 1999, in which the availability of a proposed rule amending the regulations covering supplements and other changes to an approved application under 21 CFR 314.70 was announced. Rhône-Poulenc Rorer is pleased to have the opportunity to comment officially on the proposed rule. Our comments are being submitted in duplicate to Docket 99N-0193.

Rhône-Poulenc Rorer appreciates the Agency's energy in re-writing the proposed rule. By working together, we can accomplish the goal and intent of the Food and Drug Modernization Act of 1997 (FDAMA) to streamline the regulatory approval process.

To facilitate FDA review, a table is appended which lists specific comments by CFR reference. Our general concerns with the proposed rule are as follows:

General Comments

1. Some of the requirements included in the propose rule exceed those promulgated under 21 CFR 314.70. For example, the definition provided in the proposed rule requires the sponsor to "validate the effects" of a change. The terminology "validate" creates undue confusion as most changes are validated in accordance with 21 CFR 211 "Good Manufacturing Practices for Human Drugs and Biologics."

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The goal of the proposed rule should be consistent with the intent of FDAMA, to reduce the number of manufacturing changes subject to supplements requiring FDA approval prior to distribution of the product and to significantly reduce the regulatory burden to applicants implementing such changes.

2. The proposed rule is inconsistent with other final and/or proposed draft guidance documents that have been publicly issued, namely draft guidance BACPAC-I, draft guidance for Stability Testing of Drug Substance and Drug Product, and SUPAC guidance documents. This creates an undue burden on sponsors and does not constitute an improvement in the regulatory process. Rhône-Poulenc Rorer recommends that all affected guidance documents be revised within 60 days after the Federal Register announcement of the final rule for 21 CFR 314.70.

3. The proposed rule has introduced new reporting categories and requirements that have not been included under the current regulations. For example, comparability protocols must be submitted as a prior approval supplement. This creates an undue burden on the sponsor because the proposed change could be implemented and approved in the times it takes for approval and execution of the protocol. Rhône-Poulenc Rorer recommends a less stringent reporting category (e.g. CBE-30) for review and approval of protocols. Additionally, Rhône-Poulenc Rorer recommends that the planned guidance on comparability protocols contain specific examples of acceptable comparability protocols.

As publicly requested by Dr. Eric Sheinin, Acting Deputy Director, Office of Pharmaceutical Science, at the Public Meeting held on August 19, 1999 at the Hilton Hotel, Gaitherburg, MD, an electronic copy of our comments will be transmitted to Nancy Sager, Ph.D., Associate Director, Office of Pharmaceutical Science.

We trust that our comments will be taken into consideration prior to the final issuance of the proposed rule. Should you have any questions please feel free to contact the undersigned at (610) 454-3364 or Bridgette Speights, Manager CMC Conformance at (610) 454-8440.

Sincerely,

Bridgette Speights /for

Dennis Jurgens
Associate Director, Regulatory Affairs
CMC Conformance

Specific Comments- FDA's Proposed Rule
"Supplements and Other Changes to an Approved Application"
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CFR Reference	Comment
General	Will section 314.70 contain references to the appropriate guidance documents throughout? Although there are some references to sterile products within the proposed revision to 314.70, there are many areas which are not addressed. When will the PAC SAS guidance be issued?
III. Summary of Legislation	
1&2	Use of the word "validate in this context creates confusion. We recommend the word "assess."
5	"There is a corresponding need to retain such flexibility in the proposed regulations implementing section 506A of the act to ensure that the least burdensome means for reporting changes are available." As drafted, the reporting requirements of some types of changes has become more (not less) burdensome. For example, currently, the expiration dating period may be extended based upon real time data obtained from a protocol approved in the application (scale not defined). As drafted, an expiration dating period extension must be based upon full production size lots only. Similarly, currently any change made to comply with an official compendium is reported via annual report. As drafted, the reporting of this type of change via annual report is further restricted to those changes in "official compendium that is consistent with FDA requirements and provides increase assurance...."
IV. Description of the Proposed Rule	
A. Definitions	
21 CFR 314.70 (a)	The definition of "validate the effects of the change." The choice of the phrase "validate the effects of the change" is unfortunate in that this is easily confused with the normal use of the term "validation" as relates to process or method validation. To avoid confusion, another term such as "evaluate" or "assess" should be chosen for the new definition.

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CFR Reference	Comment
B. Changes to an Approved Application	
21 CFR 314.70 (a)(6)	The requirement to list all the changes in an annual report in the cover letter is overly burdensome. Per FDA "Guidance for Industry: Format and Content of the CMC Section of an Annual Report", issued September 1994, the sponsor is required to provide a brief summary of all changes made to the application. Therefore, this information is readily available for quick review, and does not need to be repeated in the cover letter.
C. Changes Requiring a Supplement Submission and Approval Prior to Distribution of the Product Made Using the Change (Major Changes)	
General	This section is not consistent with the intent of FDAMA, as there are several new categories of changes that require prior-approval from the Agency. This would be an increase regulatory burden on Industry Sponsors. Examples are provided below.
21 CFR 314.70 (b)(2) 1.	Changes in the formulation of the drug, including inactive ingredients, requiring a prior-approval supplement is inconsistent with SUPAC.
21 CFR 314.70 (b)(2) 2.	"Changes requiring completion of studies." When the product is a true solution, changes to the manufacturing process (not formulation) are highly unlikely to change the formulation and additional clinical (BE) studies should not always be required.
21 CFR 314.70 (b)(2) 3.	"Changes that may affect product sterility assurance such as changes in product or component sterilization method(s) or an addition, deletion or substitution of steps in an aseptic processing operation .....require prior approval." Addition of a second filter in the process which is exactly the same as the current filter should require re-validation but should not be necessarily a pre-approval supplement. A CBE filing should be an acceptable approach. Also, an increase in the size of the filter (not change to the pore size) in order to accommodate a scale up < 10 fold, should also be considered for CBE status. A change only in filter size should be allowed to be reported in the annual report.

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CFR Reference	Comment
21 CFR 314.70 (b)(2) 4.	Changes in the synthesis or manufacture of the drug substance requiring a prior-approval supplement is inconsistent with draft guidance BACPAC-I. "Changes in the synthesis of manufacture...." It be more appropriate to list these as "Changes in the **route** of synthesis or...." Changes such as an additional recrystallization step (using the same solvents, etc.) should be considered for CBE status.
D. Changes Requiring Supplement Submission at Least 30 Days Prior to Distribution of the Drug Product Made Using the Change (Moderate Changes)	
General	Both 30 day CBE and CBE immediate implementation are defined as "Moderate Changes" Can there be different verbiage for these two categories to allow differentiation?
E. Changes That May Be Implemented When FDA Receives a Supplement (Moderate Changes)	
21 CFR 314.70 (c)(6) 1.	Minor changes, considered improvements to the method, that can be shown to provide the same or greater level of assurance of the ID, strength, quality, purity and potency should be considered to have a minimal potential to have an adverse effect and should be allowed to be filed in the Annual Report and not CBE-0.
F. Changes To Be Described in the Next Annual Report (Minor Changes)	
21 CFR 314.70 (d)(2) 1.	All changes made to comply with an official compendium should continue to be filed in the annual report. The addition of language "consistent with FDA requirements" allows for individual reviewer interpretations and inconsistent enforcement of the regulation.
21 CFR 314.70 (d)(2) 6.	The use of "full production batches" to extend expiry dating is unnecessary for a new product as the application was likely approved using less than commercial size batches. The extension of the expiration date on three pilot scale batches tested in accordance with the approved stability protocol should be allowed to be reported in the Annual Report.

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CFR Reference	Comment
F. Other Information	
21 CFR 314.70 (e)	Comparability protocols require prior approval. This may be construed as an increased regulatory burden if the applicant has to file a prior approval supplement. Comparability protocols should be reviewed by the Agency within a reasonable amount of time to allow the applicant sufficient time to implement the change. Our recommendation is to submit comparability protocols as a CBE-30 day. We also recommend that the Agency issue a guidance document which includes specific examples of comparability protocols that are approvable in the Agency's opinion.

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